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Synthesis of Chiral N-Alkyl-Cyclopentadienyl Sulfonamides

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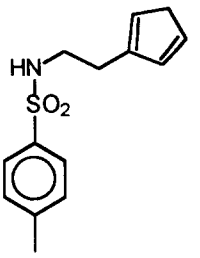
Abstract: The reaction of sodium cyclopentadiene or lithium indene with tosylamino tosylates of amino alcohols yield a series of novel N-alkylcyclopentadiene sulfonamides. These cyclopentadiene derivatives are potential ligands capable of chelating to transition metals. Optically active derivatives were prepared starting from chiral β-amino alcohols.

Introduction

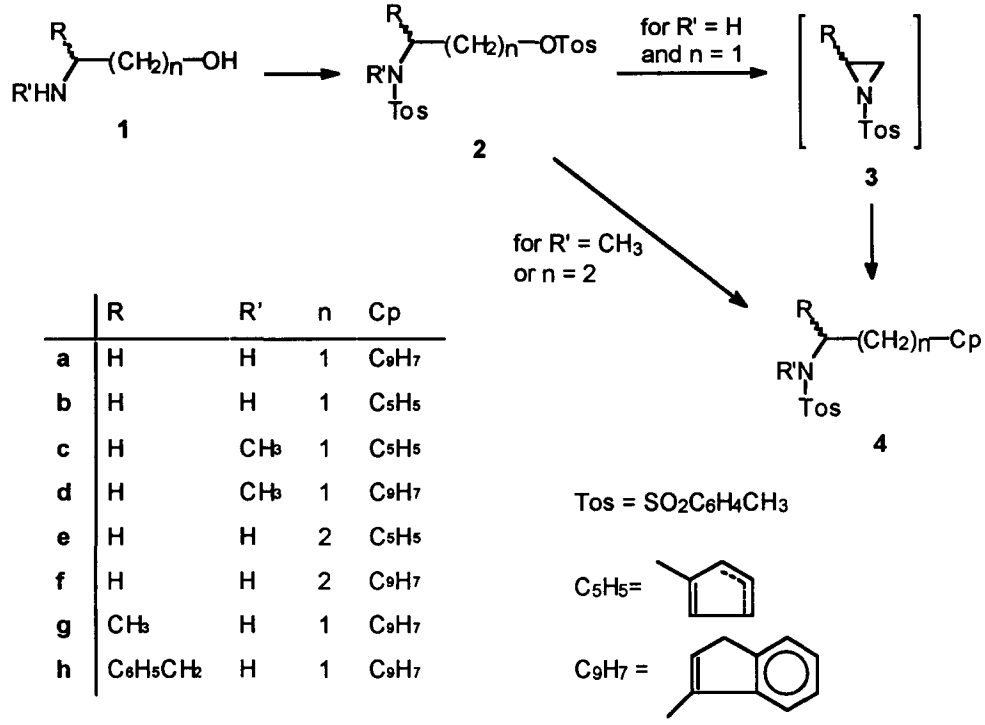
The cyclopentadienyl ligand is an important ligand in organometallic chemistry because it will complex a wide range of transition metals.[1] Recently there has been an increased attention to cyclopentadiene ligands containing pendant groups that are capable of coordinating to a metal centre as well. Examples of these bidentate ligands are cyclopentadiene ligands containing amine[2,3], ether[4], amido[5,6] and alkoxy[7] pendant groups.

The asymmetric catalytic properties of cyclopentadiene metal complexes are also receiving more attention. Different strategies have been developed to introduce asymmetry in cyclopentadiene metal complexes.[8] Examples of these strategies are the use of cyclopentadiene ligands with a chiral substituent connected to the cyclopentadiene ring[9], the use of annulated chiral cyclopentadiene ligands[1,10] and the use of *ansa*-bridged bis-indenyl ligands in which the group bridging the two indenyls is either achiral[11] or chiral.[12] Chiral cyclopentadiene ligands containing a pendant donor have been described in only a few papers.[4,13] Recently the synthesis of a chiral cyclopentadiene ligand based on ephedrine and pseudo ephedrine was described.[14]

Ligands containing sulfonamido groups are also known and have been employed successfully in a number of asymmetric reactions catalysed by titanium.[15,16] In this paper we describe the synthesis of a group a cyclopentadiene ligands that contain a *p*-toluenesulfonamide as the pendant group. These ligands are accessible from amino alcohols in a simple two step synthesis (scheme 1).



Scheme 1

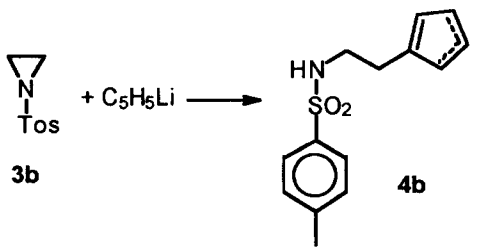


	R	R'	n	Cp
a	H	H	1	C_9H_7
b	H	H	1	C_5H_5
c	H	CH_3	1	C_5H_5
d	H	CH_3	1	C_9H_7
e	H	H	2	C_5H_5
f	H	H	2	C_9H_7
g	CH_3	H	1	C_9H_7
h	$C_6H_5CH_2$	H	1	C_9H_7

Results and Discussion

The reaction of lithium indenyl with the tosylamino tosylate of ethanolamine (**2a**) yields the N-ethyleneindene sulfonamide **4a** as indicated (scheme 1). Compound **4a** was obtained as a single isomer. The single crystal X-ray crystallographic structure determination is reported elsewhere.[17] This reaction most likely proceeds via an aziridene intermediate **3a**[18] and as expected, the reaction of N-tosyl aziridine **3a**, readily obtained from **2a** by the reaction with KOH[19], with lithium indene also yields **4a**. The reaction of sodium cyclopentadiene with **3b** gives the cyclopentadiene derivative **4b** which was isolated as a 1:1 mixture of two

Scheme 2



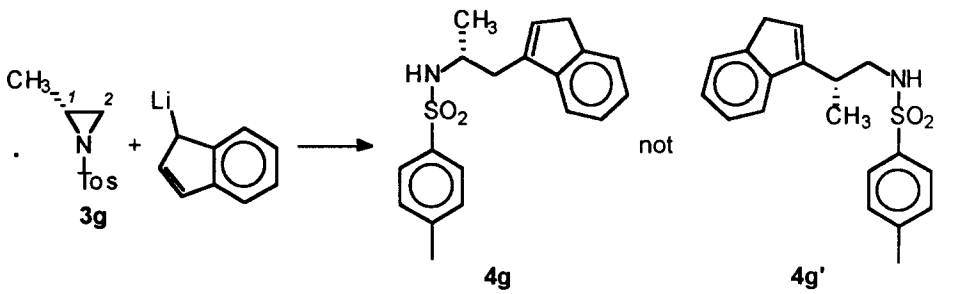
regioisomeric dienes (scheme 2).

The synthesis of cyclopentadienyl sulfonamides was further expanded to include N-methyl derivatives **4c-d** and derivatives of 1,3-propanolamine **4e-f**. All reactions proceed with reasonable yields in the range of 40-80 %. The reaction with lithium indenyl gives, on average, a higher yield and only one isomer when compared with the reaction of sodium cyclopentadienyl. The reactions with sodium cyclopentadienyl all result in the formation of a 1:1 mixture of regioisomeric dienes.

The indenyl sulfonamide ligands are prochiral ligands and will, when complexed to a metal centre, result in the formation of a racemic mixture. The use of a chiral indenyl sulfonamide should yield a mixture of two diastereomeric metal complexes and may possibly be diastereoselective.[12] Homochiral derivatives of **4** are accessible from tosylated homochiral amino alcohols such as **1g-h.** These alcohols can be easily obtained from naturally occurring enantiomerically pure amino-acids.

The reaction of indenyl lithium with the p-toluenesulfonyl derivative of (**R**)-2-amino-1-propanol could, in theory, result in the formation of two products, one from the substitution at C-1 , the other resulting from the substitution at C-2, assuming that the reaction proceeds via the aziridenyl intermediate **3g** (scheme 3). In fact, only the expected product[20] **4g** , i.e. substitution at C-2 is observed and isolated in high yield. The same substitution and high yield was observed for the reaction of the indenyl anion with the tosylated (S)-2-amino-3-phenyl-1-propanol **4h**.

Scheme 3



The coordination chemistry of these novel cyclopentadiene ligands is currently the subject of further investigations and will be reported in due course.

Experimental

NMR spectra were recorded on a Bruker AC300 spectrometer. Handling of organometallic reagents was carried out under an inert atmosphere of argon using standard Schlenk techniques. All synthesis were carried out using a similar procedure. The procedures for compound **4a** and **4b** are typical.

4a: Freshly distilled indene (3.74 g, 32.6 mmol) was dissolved in dry THF (100 mL) and cooled to -78 °C. ^{n}BuLi (13 mL, 1.6 M) was added via syringe. The reaction mixture was allowed to warm to 0 °C. The reaction mixture was subsequently cooled to -40 °C and **3a** (4.0 g, 20.3 mmol) was added as a solid in one portion. The reaction mixture was allowed to warm slowly to room temperature and stirred for 17h. Saturated NH_4Cl (100 mL) was added to the reaction mixture followed by ethyl acetate (50 mL). The organic layer was separated from the aqueous layer, washed with brine and dried on Na_2SO_4. The solvent was removed *in vacuo* to yield a tan coloured solid. Recrystallization from hexanes/ethyl acetate (2/1) yielded **4b** as off-white crystals (4.06 g, 64 %). (Found; C, 68.81; H, 6.11; N, 4.47; S, 10.21. $C_{18}H_{19}NO_2S$ requires C, 68.98; H, 6.11; N, 4.47; S, 10.23 %). δ_H ($CDCl_3$) 2.31 (3H, s, CH_3), 2.64 (2H, dt, J 1.4 Hz and 6.8 Hz, $NCH_2C\underline{H}_2$), 3.20 (q, 2H, J 6.8 Hz, NCH_2), 3.21 (s, 2H, CH_2(indene)), 4.60 (t, 1H, J 6.0 Hz, NH), 6.11 (s, 1H, CH(indene)) 7.12 (m, 3H, CH_{arom}(indene)), 7.14 (d, 2H, J 8.0 Hz, CH_{arom}(tosyl)), 7.35 (m, 1H, CH_{arom}(indene)), 7.61 (d, 2H, J 8.0 Hz, CH_{arom}(tosyl)); δ_C ($CDCl_3$) 21.5 (CH_3), 28.0 (CH_2(indene)), 37.9 ($NCH_2\underline{C}H_2$), 41.4 ($N\underline{C}H_2CH_2$), 118.7, 123.9, 124.90, 126.1, 127.0, 129.6, 130.2, 136.9, 140.2, 143.3, 144.3, 144.3.

Alternatively **4a** can be prepared from LiC_9H_7 (21.3 mmol) and **2a** (2.50 g, 6.77 mmol). Yield 1.61 g, 76 %. The product had ^1H and ^{13}C spectra identical to the product described in the previous procedure.

4b: To a solution of NaC_5H_5 (37 mmol, prepared from NaH and C_5H_6) in THF (20 mL) was added dropwise a solution of **3a** (4.0 g, 20.3 mmol) in THF (10 mL). The reaction mixture was stirred overnight at room temperature. A saturated solution of NH_4Cl (20 mL) was added to the reaction mixture. The organic phase was separated from the aqueous phase. The aqueous phase was extracted with ethyl acetate. The combined organic phases were concentrated under reduced pressure to yield a brown oil (2.34 g) The oil was subjected to column chromatography (silica-60, ethyl acetate/hexanes 1/3). Compound **4b** was isolated as a mixture of two isomers as a pale yellow oil which crystallized on standing (2.60 g, 48 %). (Found; C, 63.20; H, 6.51; N, 5.39; S, 11.80. $C_{14}H_{17}NO_2S$ requires C, 63.85; H, 6.51; N, 5.32; S, 12.17). δ_H ($CDCl_3$) 2.35 (s, 3H, CH_3), 2.48 (m, 2H, $NCH_2C\underline{H}_2$), 2.68/2.85 (both d, 2H, J 1.3 Hz, CH_2(indene)), 3.05 (m, 2H, NCH_2), 4.54 (br, 1H, NH), 5.93(s), 6.07(s), 6.21(m) and 6.30(m) (these 4 signals integrate for 3H, CH of the Cp ring), 7.22 (d, 2H, J 8.1 Hz, CH_{arom}(tosyl)), 7.65 (d, 2H, J 8.3 Hz, CH_{arom}(tosyl)); δ_C ($CDCl_3$) 21.4 (CH_3), 29.6, 30.4 (CH_2(indene)), 41.4, 41.9 ($NCH_2\underline{C}H_2$), 42.6, 42.9 (NCH_2), 127.0, 128.5, 128.9, 131.7, 132.1, 133.5, 134.7, 136.8, 136.9, 142.5, 143.3, 144.3.

4c: From NaC_5H_5 (15 mmol) and **2c** (3.80 g, 10.0 mmol), chromatography (silica-60, ethyl acetate/hexanes 1/3). Compound **4c** was isolated as a mixture of two isomers as a pale yellow oil which crystallized on standing (1.15 g, 41 %); δ_H ($CDCl_3$) 2.42 (s, 3H, CH_3), 2.63 (m, 2H, $NCH_2C\underline{H}_2$), 2.73/2.75 (both s, 3H, NCH_3), 2.91/2.95 (both d, 2H, J 1.4 Hz, CH_2), 3.20 (q, 2H, J 7.8 Hz, NCH_2), 6.08 (t, J 1.5 Hz), 6.22(s) 6.29 (d, J 5.2 Hz), 6.40(d, J 1.6 Hz), 6.42 (d, J 1.7 Hz) (these signals integrate for 3H, CH of the Cp

ring), 7.22 (d, 2H, J 8.1 Hz, CH_{arom}(tosyl)), 7.65 (d, 2H, J 8.3 Hz, CH_{arom}(tosyl)); δ_C ($CDCl_3$) 21.3 (CH_3), 28.4, 28.9 (CH_2), 34.5, 34.7 ($NCH_2\underline{C}H_2$), 41.2, 43.1 (NCH_2), 49.5, 49.9 (NCH_3),127.2, 127.7, 128.2, 129.4, 131.3, 132.1, 133.9, 142.8, 143.0.

4d: From LiC_9H_7 (12.8 mmol) and **2d** (2.0 g, 5.2 mmol), chromatography (silica-60, hexanes/ethyl acetate 3/1). Compound **4d** was recrystallized from hexanes/ethyl acetate (1.06g, 62%). (Found; C, 69.44; H, 6.66; N, 4.42; S, 9.78. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.46; N, 4.28; S, 9.79. δ_H ($CDCl_3$) 2.40 (s, 3H , CH_3), 2.81 (s, 3H, NCH_3), 2.82 (dt, 2H, J 8.0 Hz and 1.4 Hz, $NCH_2C\underline{H}_2$), 3.31 (s, 2H, CH_2(indene)), 3.33 (t, 2H, J 7.5 Hz, NCH_2), 6.29 (s, 1H, CH(indene)), 7.24 (m, 3H, CH_{arom}(indene)), 7.27 (d, 2H, J 8.0 Hz, 2H, CH_{arom}(tosyl)), 7.44 (d, 1H, J 7.3 Hz, CH_{arom}(indene)), 7.66 (d, 2H, J 7.3 Hz, CH_{arom}(tosyl)). δ_C ($CDCl_3$) 26.5 (CH_3), 26.8 (CH_2(indene)), 35.0 ($NCH_2\underline{C}H_2$), 37.9 ($N\underline{C}H_2CH_2$), 49.1 (NCH_3),118.7, 123.8, 126.1, 127.3, 129.6, 129.7, 134.8, 140.6, 143.2, 144.2, 144.7.

4e: From NaC_5H_5 and **2e** (3.40 g, 8.9 mmol), chromatography (silica-60, hexanes/ethyl acetate 2:1) to yield **4e** as an 1:1 mixture of two isomers (0.80 g, 33 %); δ_H ($CDCl_3$) 1.70 (q, 1H, J 7.3 Hz, CH_2), 1.71 (q, 1H, J 7.1 Hz, CH_2), 2.37 (m, 2H, $NCH_2C\underline{H}_2$), 2.43 (s, 3H, CH_3), 2.80 (d, 2H, J 1.2 Hz, $CH{=}C\underline{H}_2$), 2.92 (d, 2H, J 1.5 Hz, $CH{=}C\underline{H}_2$), 2.97 (q, 2H, J 5.7 Hz, NCH_2), 4.46 (br, 1H, NH), 5.95-6.34 (m, 3H, CH=C), 7.30 (d, 2H, J 8.1 Hz, CH_{arom}(tosyl)), 7.73 (d, 2H, J 8.2 Hz, CH_{arom}(tosyl)).

4f: From LiC_9H_7 (30 mmol) and **2f** (5.0g, 13.1 mmol), chromatography (silica gel 60, ethyl acetate/hexanes 1/2) and recrystallized to yield **4f** (2.65 g, 62 %). (Found; C, 69.59; H, 6.69; N, 4.26; S, 9.80. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.46; N, 4.28; S, 9.79). δ_H ($CDCl_3$) 1.84 (m, 2H), 2.40 (s, 3H, CH_3), 2.53 (dt, 2H, J 1.5 and 7.4 Hz), 3.03 (q, 2H, J 6.6 Hz, NCH_2), 3.27 (d, 2H, J 1.7 Hz, CH_2(indene)), 6.12 (s, 1H, CH(indene)), 7.25 (m, 3H, CH_{arom}(indene)), 7.26 (d, 2H, J 8.2 Hz, CH_{arom}(tosyl)), 7.43 (d, 1H, J 7.1 Hz, CH_{arom}(indene)), 7.73 (d, 2H, J 8.3 Hz, CH_{arom}(tosyl)); δ_C ($CDCl_3$) 21.5 (CH_3), 24.6 (CH_2), 27.8 (CH_2(indene)), 37.7 ($NCH_2\underline{C}H_2$), 42.9 ($N\underline{C}H_2CH_2$), 118.8, 123.8, 124.7, 126.0, 127.1, 128.4, 129.7, 137.0, 142.9, 143.3, 144.4, 144.9.

4g: From LiC_9H_7 (20 mmol) and **2g** (1.65 g, 4.30 mmol) prepared by tosylation of **(R)**-(-)-2-amino-1-propanol, chromatography (silica-60, ethyl acetate/hexanes 2/5). The product was isolated a pale brown oil (1.24 g, 88 %). $[\alpha]_D$: -32.1 (c = 0.42, $CHCl_3$); δ_H ($CDCl_3$) 1.14 (d, 3H, J 6.4 Hz, $CHC\underline{H}_3$), 2.26 (s, 3H, $C_6H_5C\underline{H}_3$), 2.55 (dd, 1H, ^2J 14.1 Hz, ^3J 6.6 Hz, $NCHC\underline{H}_a$), 2.61 (dd, 1H, ^2J = 14.1 Hz, ^3J = 7.1 Hz, $NCHC\underline{H}_b$), 3.16 (s, 2H, CH_2(indene)), 3.51 (m, 1H, NCH), 4.38 (d, 1H, J 6.3 Hz, NH), 6.10 (s, 1H, CH(indene)), 6.98-7.60 (m, 8H). δ_C ($CDCl_3$) 21.4 ($C_6H_5\underline{C}H_3$), 22.1 ($NCH\underline{C}H_3$), 35.9 ($NCH\underline{C}H_2$), 37.8 (CH_2(indene)), 48.4 (NCH), 118.9, 123.7, 124.6, 126.0, 126.7, 129.3, 131.2, 137.1, 140.0, 142.9, 144.2.

4h: From LiC_9H_7 (20 mmol) and **2h** (1.70 g, 3.98 mmol) prepared by tosylation of (S)-(-)-2-amino-3-phenyl-1-propanol, chromatography (silica-60, ethyl acetate/hexanes 1/3). The product was further purified by recrystallization from warm ethyl acetate/hexanes (1/10) (1.34g, 79 %). $[\alpha]_D$: +23.3 (c = 0.37, $CHCl_3$); (Found; C, 74.38; H, 6.42; N, 3.72; S, 7.95. $C_{25}H_{25}NO_2S$ requires C, 74.41; H, 6.24; N, 3.47; S, 7.94). δ_H ($CDCl_3$) 2.21 (s, 3H, CH_3), 2.57 (dd, 1H, ^2J 14.4 Hz, ^3J 7.9 Hz, NCHC$\underline{H}_a$), 2.65 (dd, 1H, ^2J = 14.4 Hz, ^3J = 5.9 Hz, NCHC$\underline{H}_b$), 2.81 (dd, 1H, ^2J 13.7 Hz, ^3J 6.9 Hz, $C_6H_5C\underline{H}_a$), 2.89 (dd, 1H, ^2J 13.7 Hz, ^3J 5.7 Hz, $C_6H_5C\underline{H}_b$), 3.11 (d, 2H, J 6.5 Hz, 2H, CH_2(indene)), 3.58 (m, 1H, NCH), 4.35 (br, 1H, NH), 6.09 (s, 1H, CH(indene)), 6.84-7.41 (m, 13H); δ_C ($CDCl_3$) 21.5 (CH_3), 33.2 ($C_6H_5\underline{C}H_2$), 37.9 (CH_2(indene)), 41.8 (NCH$\underline{C}H_2$), 53.7 (NCH), 119.1, 123.8, 124.8, 12 6.2, 126.7, 128.7, 129.1, 129.3, 129.7, 131.4, 140.2, 142.9, 144.3.

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